REMARKS

The specification has been amended as listed below. Support for these amendments may be found throughout the specification, and for instance as noted below:

Location of Amendment	Amendment	Support in Specification
Page 4, lines 19-22	LEN L-CDR1 and LEN L-CDR2 correspond to SEQ ID NOs: 7 and 8, respectively	Original Figure 2.
Page 5, lines 3-6	. . . and humanized MAb HuCC49 with the corresponding CDR sequences of . . .	Page 3, lines 21-26; page 10, lines 25-30; and page 12, lines 3-5
	CDR1, CDR2 and CDR3 within the light chain of HuCC49 and CC49 correspond to SEQ ID NOs: 1-3, respectively.	Original Figure 2 and, with respect to CC49, page 3, lines 21-26; page 5, line 3; page 10, lines 25-30; and page 12, lines 3-5
	CDR1, CDR2 and CDR3 within the heavy chain of HuCC49 and CC49 correspond to SEQ ID NOs: 4-6, respectively.	Original Figure 2 and, with respect to CC49, page 3, lines 21-26; page 5, line 3; page 10, lines 25-30; and page 12, lines 3-5
	CDR1, CDR2 and CDR3 within the light chain of human antibody LEN correspond to SEQ ID NOs: 7-9, respectively.	Original Figure 2
	CDR1, CDR2 and CDR3 within the heavy chain of human antibody 21/28'CL correspond to SEQ ID NOs: 10-12, respectively.	Original Figure 2

Page 6, lines 22-26	SEQ ID NO: 13 SEQ ID NOs: 33-36	Original Figure 11A
	SEQ ID NO: 14 SEQ ID NOs: 37-40	Original Figure 11B
Page 6, lines 27-32	SEQ ID NO: 41 SEQ ID NO. 42	Original Figure 12A
	SEQ ID NO: 43 SEQ ID NO. 44	Original Figure 12B
	The four overlapping oligomers depicted by long arrows in Figure 12A are represented by SEQ ID NOs: 19-22.	Original Figure 12A
	The four overlapping oligomers depicted by long arrows in Figure 12B are represented by SEQ ID NOs: 15-18.	Original Figure 12B
Insertion of brief description of sequence listing at page 7, line 29	SEQ ID NOs: 1-6	Original Figure 2 and, with respect to CC49, page 3, lines 21-26; page 5, line 3; page 10, lines 25-30; and page 12, lines 3-5
	SEQ ID NOs: 7-12	Original Figure 2
	SEQ ID NO: 13	Original Figure 11A
	SEQ ID NO: 14	Original Figure 11B
	SEQ ID NOs: 15-18	Original Figure 12B and page 19, line 17-19
	SEQ ID NOs: 19-22	Original Figure 12A
	SEQ ID NOs: 23-26	Page 20, lines 8-13
	SEQ ID NOs: 27-32	Page 29, lines 25-27 and page 30, lines 1-15
	SEQ ID NOs: 33-36	Original Figure 11A

	SEQ ID NOs: 37-40	Original Figure 11B
	SEQ ID NOs: 41 and 42	Original Figure 12A
	SEQ ID NOs: 43 and 44	Original Figure 12B
Page 19, lines 3-12	All amendments this paragraph	Original Figure 2
Page 19, lines 15-28	All amendments this paragraph	Original Figure 12B
Page 19, lines 31-35, and page 20, lines 1-17	All amendments this paragraph	SEQ ID NOs. correspond to the sequences originally listed at page 20, lines 10-13 in the text.
Page 30, lines 22-27, and page 31, lines 1-15	All amendments this paragraph	SEQ ID NOs. correspond to the sequences originally listed at page 31, lines 2-15 in the text.

The specification has been further amended to clarify the labeling of page 2/23 of the drawings as originally filed. Support for amendment of page 2/23 of the drawings can be found throughout the specification, and for instance on page 3, lines 21-26, page 5, line 3, page 10, lines 25-30, and page 12, lines 3-5.

Sequence identifiers are inserted in the original specification and original claims in compliance with 37 C.F.R. § 1.821(d).

The corrected sequence listing is submitted solely to comply with the requirements of 37 C.F.R § 1.821-1.825.

No new matter is added by any of the foregoing amendments.

CONCLUSIONS

If any minor matters remain to be discussed prior to examination, the Examiner is invited to contact the undersigned at the telephone number listed below.

Respectfully submitted,

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Marked-up Version of Amended Specification
Pursuant to 37 C.F.R. §§ 1.121(b)-(c)

In the Specification:

Please replace the paragraph at page 4, lines 19-22 with the following:

In particular, the invention relates to variants of HuCC49 in which either L-CDR1 or L-CDR2, or both, are from a human monoclonal antibody (LEN) (LEN L-CDR1 and LEN L-CDR2 correspond to SEQ ID NOs: 7 and 8, respectively). These variants of HuCC49 have the substantially the same affinity constant as HuCC49, or show only a two fold lower relative affinity than that of HuCC49.

Please replace the paragraph at page 5, lines 3-6 with the following:

Figure 2 shows a comparison of the CDR sequences of murine MAb CC49 and humanized MAb HuCC49 with the corresponding CDR sequences of~~and~~ human MAbs LEN and 21/28'CL. Amino acid residues are numbered using the convention of Kabat et al. The underlined numbers indicate the specificity determining residues (SDRs). CDR1, CDR2 and CDR3 within the light chain of HuCC49 and CC49 correspond to SEQ ID NOs: 1-3, respectively. CDR1, CDR2 and CDR3 within the heavy chain of HuCC49 and CC49 correspond to SEQ ID NOs: 4-6, respectively. CDR1, CDR2 and CDR3 within the light chain of human antibody LEN correspond to SEQ ID NOs: 7-9, respectively. CDR1, CDR2 and CDR3 within the heavy chain of human antibody 21/28'CL correspond to SEQ ID NOs: 10-12, respectively.

Please replace the paragraph at page 6, lines 22-26 with the following:

Figure 11 shows the amino acid sequences of V_L frameworks of human MAb LEN (SEQ ID NOS: 33-36) and humanized V_L of CC49 (HuCC49) (SEQ ID NO: 13) in panel A. Panel B shows the amino acid sequences of V_H frameworks of human MAb 21/28'CL (SEQ ID NOS: 37-40) and humanized V_H of CC49 (HuCC49) (SEQ ID NO: 14). Framework residues that are deemed to be important in maintaining the combining site structure of CC49 are marked by an asterisk.

Please replace the paragraph at page 6, lines 27-32 with the following:

Figure 12 shows the nucleotide sequence of HuCC49 variable light (V_L) region (SEQ ID NO: 41 and SEQ ID NO: 42) and variable heavy (V_H) region (SEQ ID NO: 43 and SEQ ID NO: 44) genes in panels A and B, respectively. Sequences of flanking oligomers that do not encode the variable region domains or their leader peptides are shown in lowercase letters. The V_L region (A) is encoded by nucleotides from positions 74 to 412, while nucleotides from position 70 to 415 (B) comprise the V_H region. The four overlapping oligomers depicted by long arrows in Figure 12A are represented by SEQ ID NOs: 19-22. The four overlapping oligomers depicted by long arrows in Figure 12B are represented by SEQ ID NOs: 15-18.

Please insert the following text at page 7, line 29, immediately preceding the section entitled "Definitions":

Sequence Listing

The nucleic and amino acid sequences listed in the accompanying sequence listing are shown using standard letter abbreviations for nucleotide bases and three letter code for amino acids, as defined in 37 C.F.R. 1.822. In the accompanying sequence listing:

SEQ ID NO: 1 shows the amino acid sequence of CDR1 from the light chain of murine antibody CC49 and humanized antibody HuCC49.

SEQ ID NO: 2 shows the amino acid sequence of CDR2 from the light chain of murine antibody CC49 and humanized antibody HuCC49.

SEQ ID NO: 3 shows the amino acid sequence of CDR3 from the light chain of murine antibody CC49 and humanized antibody HuCC49.

SEQ ID NO: 4 shows the amino acid sequence of CDR1 from the heavy chain of murine antibody CC49 and humanized antibody HuCC49.

SEQ ID NO: 5 shows the amino acid sequence of CDR2 from the heavy chain of murine antibody CC49 and humanized antibody HuCC49.

SEQ ID NO: 6 shows the amino acid sequence of CDR3 from the heavy chain of murine antibody CC49 and humanized antibody HuCC49.

SEQ ID NO: 7 shows the amino acid sequence of CDR1 from the light chain of human antibody LEN

SEQ ID NO: 8 shows the amino acid sequence of CDR2 from the light chain of human antibody LEN

SEQ ID NO: 9 shows the amino acid sequence of CDR3 from the light chain of human antibody LEN

SEQ ID NO: 10 shows the amino acid sequence of CDR1 from the heavy chain of human antibody 21/28'CL

SEQ ID NO: 11 shows the amino acid sequence of CDR2 from the heavy chain of human antibody 21/28'CL

SEQ ID NO: 12 shows the amino acid sequence of CDR3 from the heavy chain of human antibody 21/28'CL

SEQ ID NO: 13 shows amino acids sequence of the V_L domain of the humanized murine antibody HuCC49.

SEQ ID NO: 14 shows amino acids sequence of the V_H domain of the humanized murine antibody HuCC49.

SEQ ID NOs: 15-32 show several synthetic oligonucleotides useful as probes and/or primers.

SEQ ID NOs: 33-36 show amino acid sequences of consecutive portions of the framework of the V_L domain of the human antibody LEN.

SEQ ID NOs: 37-40 shows amino acid sequences of consecutive portions of the framework of the V_H domain of the human antibody 21/28'CL.

SEQ ID NO: 41 show the nucleic acid sequence including the V_L domain of the humanized murine antibody HuCC49 together with flanking oligomers.

SEQ ID NO: 42 shows the nucleic acid sequence complementary to SEQ ID NO: 41.

SEQ ID NO: 43 shows the nucleic acid sequence including the V_H domain of the humanized murine antibody HuCC49 together with flanking oligomers.

SEQ ID NO: 44 shows the nucleic acid sequence complementary to SEQ ID NO: 43.

Please replace the paragraph at page 19, lines 3-12 with the following:

According to the invention, CDR variants are formed by replacing at least one CDR of CC49 in HuCC49 with a corresponding CDR from a human antibody. The CDR variants of the invention include:

- Variant L-1: L-CDR1 of CC49 (SEQ ID NO: 1) was replaced with L-CDR1~~that~~ of LEN (SEQ ID NO: 7).
- Variant L-2: L-CDR2 of CC49 (SEQ ID NO: 2) was replaced with L-CDR2~~that~~ of LEN (SEQ ID NO: 8).
- Variant L-3: L-CDR3 of CC49 (SEQ ID NO: 3) was replaced with L-CDR3~~that~~ of LEN (SEQ ID NO: 9).
- Variant L-1,2: L-CDR1 and L-CDR2 of CC49 (SEQ ID NOs: 1 and 2, respectively) were replaced with L-CDR1 and L-CDR2~~that~~ of LEN (SEQ ID NOs: 7 and 8, respectively).
- Variant H-1: H-CDR1 of CC49 (SEQ ID NO: 4) was replaced with H-CDR1~~that~~ of 21/28'CL (SEQ ID NO: 10).
- Variant H-2: H-CDR2 of CC49 (SEQ ID NO: 5) was replaced with H-CDR2~~that~~ of 21/28'CL (SEQ ID NO: 11).
- Variant H-3: H-CDR3 of CC49 (SEQ ID NO: 6) was replaced with H-CDR3~~that~~ of 21/28'CL (SEQ ID NO: 12).

Please replace the paragraph at page 19, lines 15-28 with the following:

Synthesis of three variant V_H genes was performed using the overlap extension PCR technique described by Kashmiri et al., (1995) Hybridoma 14:461-473. Four ~~124-137~~123-126 base pair long overlapping oligonucleotides (SEQ ID NOs: 15-18)~~.~~ (which together encompass the entire sequence of the variant V_H gene on alternating strands) were used to generate variant V_H genes. (Figure 12 B) The oligomers were supplied by Midland Certified Reagent Co., Midland, TX. Instead of a template DNA, the PCR mixture contained 2 pmoles of the four oligonucleotides. PCR was carried out by three cycles of a denaturing step at 94°C for 1 minute, a primer annealing step at 55 °C for 2 minutes, and an extension step at 70°C for 2 minutes, followed by 17 additional cycles of denaturation (94°C, 1 minute), primer annealing (55°C, 2 minutes), and extension (72°C, 1 minute). All polymerase chain reactions (PCRs) were carried

out in a final volume of 100 Tl of PCR buffer containing 100 TM of dNTPs, 5 units of Taq DNA polymerase (Boehringer Mannheim) and 20 pmol of each end primer.

Please replace the paragraph at page 19, lines 31-35, and page 20, lines 1-17, with the following:

The three variant V_L genes were generated using 30-43 base oligonucleotides as a mutagenic primer. The oligonucleotides contained the desired base changes in the targeted CDR. The mutagenic primers for the V_L genes were synthesized using a Model 8700 DNA synthesizer (Miligen/Bioresearch, Burlington, VT). (Figure 12 A) Primer induced mutagenesis was carried out by a two-step PCR method, as described by Landt et al., (1990) Gene, 96:125-128. pLNXCHuCC49HuK (Kashmiri et al, (1995) Hybridoma 14:461-473) (Figure 2) was used as a template in both steps. In the first step, the mutagenic primer was used as a 3' primer while a 20 nucleotide long end primer served as a 5' primer. The product of the first PCR was gel purified and utilized as a 5' primer for the second PCR in which a 20 nucleotide long end primer was used as a 3' primer. The 20 nucleotide long end primers used for DNA amplification were supplied by Midland Certified Reagent Co. (Midland, TX). The sequences for these primers are reported by Kashmiri et al., (1995) Hybridoma 14:461-473 and are as follows:

1. 5' V_H, 5'-CTA AGC TTC CAC CAT GGA G-3' (SEQ ID NO: 23)
2. 3' V_H, 5'-ATG GGC CCG TAG TTT GGC G-3' (SEQ ID NO: 24)
3. 5' V_L, 5'-GCA AGC TTC CAC CAT GGA TA-3' (SEQ ID NO: 25)
4. 3' V_L, 5'-AGC CGC GGC CCG TTT CAG TT-3' (SEQ ID NO: 26)

Each of the primers carries a single restriction endonuclease site at its flank. The 5' primers carry a *Hind*III site, while the 3' V_H primer carries an *Apa*I, and the 3' V_L primer has a *Sac*II site. The restriction endonuclease recognition sequences are underlined.

Please replace the paragraph at page 30, lines 22-27, and page 31, lines 1-15, with the following:

Mutagenic oligonucleotide primers, ranging in size from 37 to 56 nucleotides, were synthesized using a Model 8700 DNA synthesizer (Milligen/Bioresearch, Burlington, VT). They were purified on oligo-Pak columns (Milligen/Bioresearch) according to the supplier's recommendation. The sequences of the mutagenic primers were as follows, where the mutagenic changes are underlined:

V_L CDR3:

5'-GCC AGC GCC GAA GCT GAG GGG ATA GCT ATA ATA CTG CTG ACA-3' (SEQ ID NO: 27)

5'-GGT GCC AGC GCC GAA GCT GAG GGG GGT GCT ATA ATA CTG CTG ACA-3' (SEQ ID NO: 28)

5'-GCC ACG GCC GAA TGT GTA GGG ATA GCT ATA ATA CTG CTG ACA -3' (SEQ ID NO: 29)

5'-GCC GAA TGT GAG GGG GGT GCT ATA ATA CTG CTG ACA ATA-3' (SEQ ID NO: 30)

V_H CDR1:

5'-GTT TCA CCC AGT GCA TTG CAT AAT CAG TGA AGG TGT A-3' (SEQ ID NO: 31)

V_H CDR2:

5'-GTG GCC TTG CCC TGG AAC TTC TGT GAG TAC TTA AAA TCA TCG TTT CCG GGA GAG AA-3' (SEQ ID NO: 32)

In the Drawings:

Please replace page 2/23 of the drawings as originally filed with attached substitute page 2/23.

FIG. 2

Light chain

CDR1	24	25	26	27	a	b	c	d	e	f	28	29	30	31	32	33	34
^CC49/HuCC49	Lys	Ser	Ser	Gln	Ser	Leu	Leu	Tyr	Ser	Gly	Asn	Gln	Lys	Asn	Tyr	Leu	Ala
LEN	Lys	Ser	Ser	Gln	Ser	*Val*	Leu	Tyr	Ser	*Ser*	Asn	*Ser*	Lys	Asn	Tyr	Leu	Ala

CDR2	50	51	52	53	54	55	56
^CC49/HuCC49	Trp	Ala	Ser	Ala	Arg	Glu	Ser
LEN	Trp	Ala	Ser	*Thr*	Arg	Glu	Ser

CDR3	89	90	91	92	93	94	95	96	97
^CC49/HuCC49	Gln	Gln	Tyr	Tyr	Ser	Tyr	Pro	Leu	Thr
LEN	Gln	Gln	Tyr	Tyr	Ser	*Thr*	Pro	*Tyr*	*Ser*

Heavy chain

CDR1	31	32	33	34	35
^CC49/HuCC49	Asp	His	Ala	Ile	His
21/28'CL	*Ser*	*Tyr*	Ala	*Met*	His

CDR2	50	51	52	a	53	54	55	56	57	58	59	60	61	62	63	64	65
^CC49/HuCC49	Tyr	Phe	Ser	Pro	Gly	Asn	Asp	Asp	Phe	Lys	Tyr	Asn	Glu	Arg	Phe	Lys	Gly
21/28'CL	*Trp*	*Ile*	*Asn*	*Ala*	Gly	Asn	*Gly*	*Asn*	*Thr*	Lys	Asn	*Ser*	*Gln*	*Lys*	Phe	*Gln*	Gly

CDR3	95	96	97	98	99	100	a	b	101	102
^CC49/HuCC49	Ser	Leu	Asn	Met	Ala	-	-	-	-	Tyr
21/28'CL	*Gly*	*Gly*	*Tyr*	*Tyr*	*Gly*	*Ser*	*Gly*	*Ser*	*Asn*	Tyr